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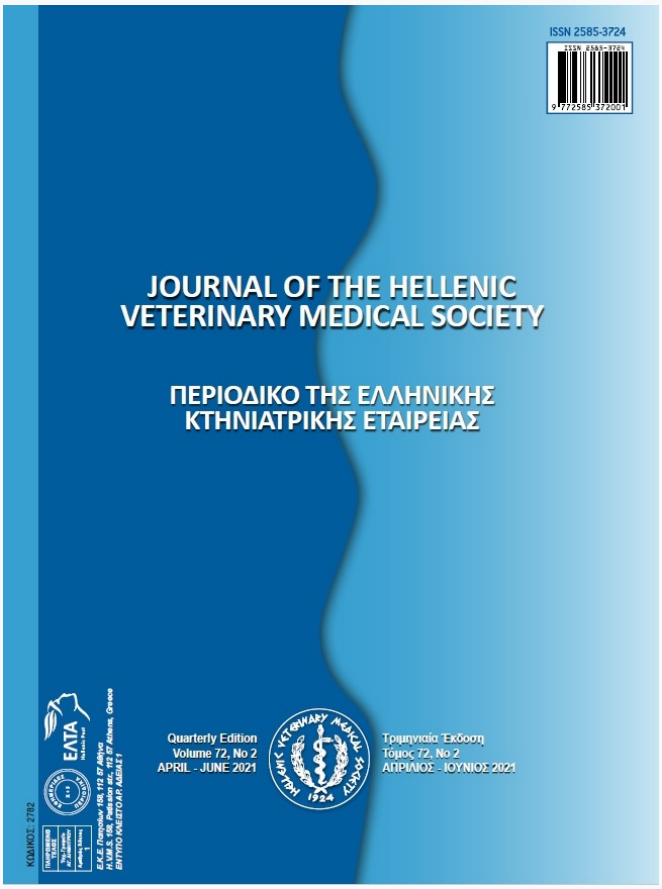

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Research article
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Pharmacokinetics and plasma concentration of thiopental in normal and stressed chickens with hydrogen peroxide

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ABSTRACT: No previous study deals with hydrogen peroxide (H_2O_2)-induced oxidative stress (OS) and its influence on thiopental anesthesia, its plasma concentration and pharmacokinetic profile in 7-14 day old chickens. OS induction was made by the daily supply of H_2O_2 from day one to the completion of the experiments on day 14th of chickens' age. Median Effective Doses (ED_{50}s) of hypnosis and analgesia were revealed an increase in thiopental efficacy by 7 and 18%, respectively in the stressed chickens in comparison to the normal one. Thiopental plasma concentration was analyzed at time 0.5, 1, 2, 4 and 24 hours after its injection at 35 mg/kg, IP to be 91.42, 54.35, 38.27, 22.30 and 7.51 µg/ml in the normal chickens and increased significantly by 74, 84, 48, 85 and 82% to be 159.01, 100.06, 56.71, 41.30 and 13.63 µg/ml in the stressed chickens, respectively. Thiopental pharmacokinetics parameters, which included Area Under the plasma Concentration ($AUC_{0-\infty}$), Area Under the Moment Curve ($AUMC_{0-\infty}$), Mean Residence Time (MRT) and elimination half-life ($t_{1/2\beta}$) were increased in the stressed chickens by 82, 94, 6 and 8%, as well as, Clearance (Cl), elimination rate constant (K_{el}), and Steady-State Volume of Distribution (V_{ss}) were decreased in the same group by 33, 14 and 41%, respectively. The results of this trial concluded that OS status intensifies thiopental anesthetic action mainly by increasing its plasma concentration and altering the pharmacokinetics profile, suggesting veterinarians to bear in mind when preparing the dose of thiopental to be given to stressed animals.

Keywords: Chickens, plasma concentration, pharmacokinetics, stress, thiopental

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INTRODUCTION

Thiopental belongs to the barbiturates anesthetics that used for the induction of short duration of the general anesthesia by its mode of action resulting from the potentiation of the inhibitory neurotransmitter effect, Gamma-Aminobutyric Acid (GABA), on its $GABA_A$ receptor subtype, leading to an increase in the outflow of chloride ions inside the post-synaptic neurons that depresses the Central Nervous System (CNS) (Garcia et al., 2010; Clark et al., 2012; Naseri et al., 2017). Thiopental possesses excellent and reliable narcotic action with less efficient analgesia and muscle relaxation than other anesthetic agents like ketamine (Clark et al., 2012; Flecknell, 2015; Katzung and Trevor, 2015). H_2O_2 was used experimentally for the induction of the OS because it is well-known. A powerful oxidizing agent besides, its concentration (0.5%) and the length of treatment required to produce OS are well studied in the previous literature through its formation of free radicals that break down the vital cell components, stimulates lipid peroxidation and breaks down of proteins (including protein receptors) (Patockova et al., 2003; Sayre et al., 2008). The CNS considered more vulnerable to OS status, because of the high free radical formation, consuming a lot of oxygen, high amount of unsaturated fatty acids with less antioxidant activity (Pastore et al., 2003). The experimentally induced OS with H_2O_2 (0.5%) was found to modify the pharmacological response of some drugs that have a neuro-active mechanism like ketamine anesthesia (Mousa, 2014), diazepam and xylazine sedation (Mousa and Mohammad, 2012a;b) by pharmacodynamics interaction on their receptors and relevant pharmacokinetic interaction at a level of absorption, distribution, metabolism and elimination of the drugs which have an impact elevating drug efficacy and subsequent toxicity. The pharmacokinetics criteria of the drug are an important factor ensuring the drug delivery to the site of action on its target receptor to achieve efficacy and/or improve the preferred therapeutic effect with minimizing its adverse effect (Wen et al., 2015).

The purpose of this study was to use thiopental in normal chickens for the induction of the general anesthesia and to determine the possible efficacy of OS-induced by H_2O_2 at thiopental anesthesia, its plasma concentration and the pharmacokinetics profile.

MATERIALS AND METHODS

Animals

7-14-days old of broiler chickens (76 overall chickens used in all the experiments) for both genders were used in all the study experiments with a regular bodyweight of 80–125 g. They were kept in cages at an ideal condition of 32–35°C and the floor of the cages comprising woody shreds. Chickens have admitted to the water and food ration freely. Thiopental [Thiopentone (Thiopental sodium), 2.5%, Egyptian International Pharmaceutical Industries Co, Egypt] diluted using normal saline solution (0.9% NaCl) to be injected by a dosage volume 5 ml/kg. The route of administration of thiopental was intraperitoneally (IP) as mentioned by a previous study in the chicks (Church, 1957).

Ethical considerations

This research and the use of experimental chickens have been valid, qualified and authenticated by the professional scientific board of the Veterinary Medicine College / Mosul University, according to international standards.

Induction of OS in the chickens

Chickens gotten from a native hatchery at one day old, divided randomly to control normal group that provided with tap water (H_2O group) whereas the other remaining chickens had treated with 0.5% H_2O_2 (50%, Scharlab, Spain) in drinking water (stressed or H_2O_2 group). The earlier studies authenticated that a continuous daily fresh supply of 0.5% H_2O_2 in tap water can prompt OS whenever assumed to chickens from 1st day and continued for 14 days. Then, H_2O_2 can prompt OS on the 7th, 10th and 14th days of chickens' lifetime through glutathione reduction and malondialdehyde raising in their concentrations at the chickens' brain and plasma (OS biomarkers) (Mousa and Mohammad, 2012a; Mousa, 2014; Kabirian et al., 2018; Aksoy and Alper, 2019). So that, 7-14-days of chickens' lifetime, were used in the current study.

Assessment of thiopental ED_{50}s in normal and stressed chickens

A. Thiopental hypnotic ED_{50} in chickens

The hypnotic ED_{50} value of thiopental was estimated in the normal and stress chickens, implement to the up-down technique mentioned earlier (Dixon, 1980). The first dosage for thiopental at 35 mg/kg, IP depends on a preliminary study. Chickens observed individually for 4 hours waiting for the hypnotic occurrence of thiopental showed by losing the righting reflex. The dosages of thiopental then would be di-

minished or augmented 10 mg reliant on the presence or lack of the hypnotic effect, respectively (Mousa and Al-Zubaidy, 2019; Mousa et al., 2019).

B. Thiopental analgesic ED_{50} in chickens

For the normal and stressed chickens, the thiopental's analgesic ED_{50} is estimated according to the previously described routine (Dixon, 1980). The first thiopental dosage be 35 mg/kg, IP depends on an introductory study. The chickens were measured before and after 15 minutes of thiopental injection by using the electro-stimulator device (Harvard apparatus, USA), which indicated by pain perception (distress call) in the chickens (Mousa, 2019; 2020; Mousa and Al-Zubaidy, 2019), the doses of thiopental then should be reduced or raised 10 mg as look or lack of the analgesia occur (the decrease or increase in doses was chosen whereby not higher than 30% of the first dose used of thiopental for accurate results).

Thiopental plasma concentration of normal and stress chickens

A single dosage of thiopental at 35 mg/kg, IP (which resembles the ED_{100} of thiopental estimated in the previous experiment) was injected to normal and stressed chickens. Blood samples combined from the jugular vein of 5 chickens per measure time at 0.5, 1, 2, 4 and 24 hours for both the normal and stressed chicks. Then, adding the heparin (B. Braun Medical Inc, USA) (1:10) to the blood samples and undergoing centrifugation (Chalice, UK) at 3000 round per minute along with 15 minutes to get plasma samples (Chauhan et al., 2020) which then freezes at -18 °C pending spectrophotometric analysis for 72 hours.

Spectrophotometric analysis

Preparation and calibration of the thiopental standards

Thiopental standards were made of 2.5, 5, 10, 20, 40, 80 and 160 µg/ml (Gustafsson et al., 1996) by dilution with 0.5 *N* of Sodium hydroxide (NaOH) and filtration then, the absorbance by Ultra Violet (UV) spectrophotometry (Lovibond, Germany) at 330 nanometers (nm) was taken by the procedure described by Goldbaun (1948) to reveal the standard curve of the simple linear regression to calculate the thiopental concentration in the unknown plasma samples. By using the equation of the simple linear regression of thiopental standards with a coefficient of determination (R^2 = 0.8958) (Fig. 1), thiopental concentration in plasma samples can be calibrated and calculated in normal and stressed chickens (Barwick, 2003) (Figure 1) were:

y = a + bx (y = 0.0974 + 0.0017x)(Equation of the simple linear regression of thiopental standards)

y = absorbance of thiopental in the plasma samples at 330 nm

a = intercept

b = slope

x = thiopental concentration in the plasma samples (unknown)

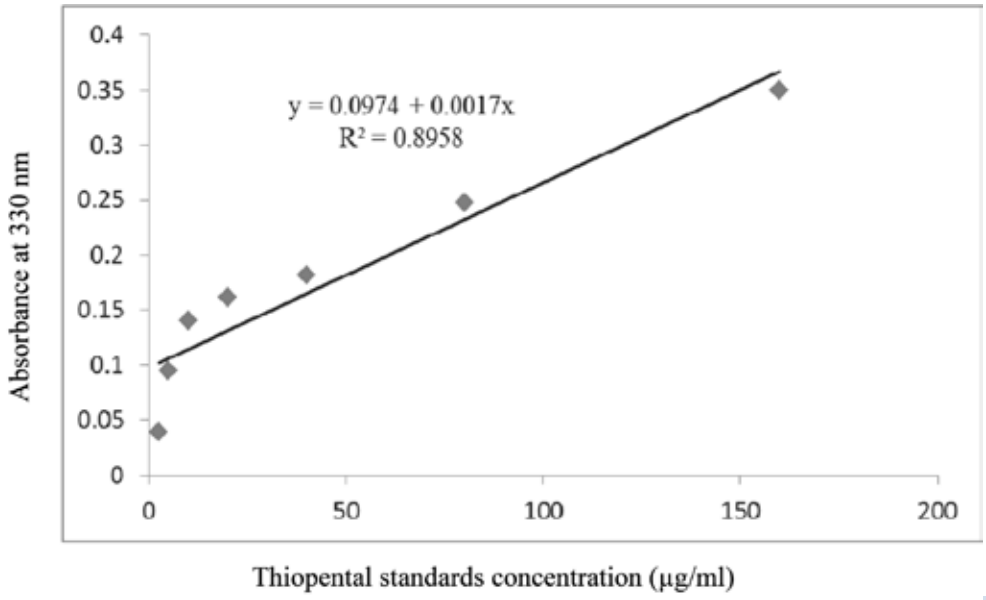

Figure 1. Equation of the simple linear regression for thiopental standards (2.5, 5, 10, 20, 40, 80 and 160 µg/ml), and their absorbance at 330 nm

Extraction and determination of thiopental in the plasma samples

A simple, validated and accurate method was used for determining thiopental concentration in the plasma (Goldbaum, 1948; Broughton, 1956) for both normal and stressed chickens in different measured times at 0.5, 1, 2, 4 and 24 hours after thiopental treatment. The procedure summarized by adding 10 ml of redistilled chloroform to 1 ml of the plasma and shake by tube shaker (Dragonlab, China) for 3 minutes. By using the filter paper, the aliquot will be obtained by using the funnel. Thereafter, 1 ml of NaOH (0.5 *N*) was added to the aliquot and the lower layer, then discarded and the remaining were centrifuged at 3000 rpm for 15 minutes to get the clear solution, which is the last consequent extraction result of the plasma sample which lastly analyzed by the UV spectrophotometry at 330 nm wavelength by using the quartz cuvette to record the absorbance for each unknown sample.

Determination of the thiopental pharmacokinetics parameters in the normal and stressed chickens

The non-compartmental method was used to find out the thiopental pharmacokinetics parameters in normal and stressed chickens by using a PKSolver program (Zhang et al., 2010) which included $AUC_{0-\infty}$ (µg.h/ml), $AUMC_{0-\infty}$ (µg.h^2/ml), MRT (AUMC/AUC)(h), Cl (dose/AUC)(L/h/kg), Tmax (h), Cmax (µg), $t_{1/2\beta}$ (h), K_{el} (0.693/ $t_{1/2\beta}$)(h^{-1}) and V_{ss} [dose. AUMC/(AUC)^2](L/kg). The increase or decrease in the percentages of the thiopental pharmacokinetics parameters was calculated in the normal chickens and correlate to determine the changes in the pharmacokinetics parameters in the stressed chickens.

Statistics

The unpaired student T-test was implemented to relate the means of two groups of parametric statistical examinations by using the SPSS program (Katz, 2011; Petrie and Watson, 2013). The data would be considered significant when $p < 0.05$.

RESULTS

Thiopental ED_{50} values the in normal and stressed chickens

A. The hypnotic ED_{50} value of thiopental

The ED_{50} values of thiopental that produce narcosis (lack of the righting reflex) in 50% of the chickens were 17.63 and 16.44 mg/kg, IP in the normal and stressed chickens, respectively, which have decreased by 7% that resembles the OS prompt by H_2O_2 to ameliorate the thiopental hypnotic ED_{50} value as determined by the up-down technique (Table 1-A) which is stated here for the first time. The signs elicited by thiopental hypnosis in the chicks were ataxia, recumbency, locked eyelids, defecation, loss of the righting reflex, paddling movements of the legs and quit sleeping with normal breathing. These signs, as it observed, it became exaggerated at the stressed chickens.

Table 1-A. Thiopental's hypnotic ED_{50} of normal and stress chickens

Parameter	Groups	
	Normal (H_2O)	Stress (H_2O_2)
Hypnotic ED_{50} value = XF + K × D	17.63 mg/kg, IP	16.44 mg/kg, IP
The extent of the doses	15-35 mg/kg	5-35 mg/kg
First dose used	35 mg/kg	35 mg/kg
Last dose used (XF)	25 mg/kg	15 mg/kg
Table Value (K) (Dixon, 1980)	-0.737	0.144
± in the dose (D)	10 mg	10 mg
Chickens used	6 (XXOXOX)*	7 (XXXOOXO)*
OS influence on thiopental hypnotic ED_{50} = H_2O- H_2O_2/ H_2O×100= 7%		

*X: effect (i.e. hypnosis), O: no effect (i.e. no hypnosis)
Tab water was given to the normal chickens while 0.5% H_2O_2 was given to the stress group from 1st to the termination of the experiments at day 14th

B. Thiopental's analgesic ED_{50} value

Thiopental antinociceptive influence in the stressed chickens with H_2O_2 was increased by 18% in association with normal chickens that have been fined by calculation of the analgesic ED_{50} value of thiopental essential to cause in 50% of the chickens to be 13.61 and 11.20 mg/kg, IP in the normal and stressed chickens, respectively that resemble the ameliorative influence of OS on the thiopental analgesic ED_{50} which is reported here for the first time in chicken and Table 1-B exemplify the various results gained from this trial.

Table 1-B. Thiopental's analgesic ED_{50} of normal and stress chickens

Parameter	Groups	
	Normal (H_2O)	Stress (H_2O_2)
Analgesic ED_{50} = XF + K × D	13.61 mg/kg, IP	11.20 mg/kg, IP
The extent of the doses used	5-35 mg/kg	5-35 mg/kg
First dose used	35 mg/kg	35 mg/kg
Last dose used (XF)	5 mg/kg	15 mg/kg
Table Value (K) (Dixon, 1980)	0.861	-0.380
± in the dose (D)	10 mg	10 mg
Chickens used	6 (XXOXXO)*	7 (XXXOOXX)*
OS influence on thiopental analgesic ED_{50} = Effect of OS= H_2O- H_2O_2/ H_2O×100= 18%		

*X: result (analgesia), O: no result (no analgesia)
Tab water was given to the normal chickens while 0.5% H_2O_2 was given to the stress group from 1st to the termination of the experiments at day 14th
Nociceptive effect recorded pre and post 15 min as thiopental treatment by using an electro-stimulator device

Thiopental plasma concentration in the normal and stressed chickens at different times

Table 2 and Figure 2 show a significant elevation in the thiopental plasma concentration of the stressed chickens compared to the normal one. The plasma concentration of thiopental measured at time 0.5, 1, 2, 4 and 24 hours after its injection at 35 mg/kg, IP were 91.42, 54.35, 38.27, 22.30 and 7.51µg/ml in the normal chickens while the plasma concentration was increased by 74, 84, 48, 85 and 82% to be 159.01, 100.06, 56.71, 41.30 and 13.63 µg/ml in the stressed chickens, respectively.

Table 2. Plasma concentration of thiopental in the normal and stressed chickens at different times

Groups	Times (Hour)				
	0.5	1	2	4	24
Normal (H_2O) (µg/ml)	91.42 ± 8.60	54.35 ± 4.95	38.27 ± 1.83	22.30 ± 2.12	7.51 ± 0.66
Stressed (H_2O_2) (µg/ml)	159.01 ± 10.19*	100.06 ± 5.54*	56.71 ± 2.85*	41.30 ± 3.90*	13.63 ± 0.75*
OS influence on plasma concentration of thiopental = Effect of OS= H_2O_2- H_2O/ H_2O×100= (%)	+74	+84	+48	+85	+82

Data represent Mean ± Standard Error for 5 chickens/measured time
Tab water was given to the normal chickens while 0.5% H_2O_2 was given to the stress group from 1st to the termination of the experiments on day 14th
Thiopental therapy 35 mg/kg, IP for both the normal and stress chickens
*: significantly different from normal group ($p < 0.05$)

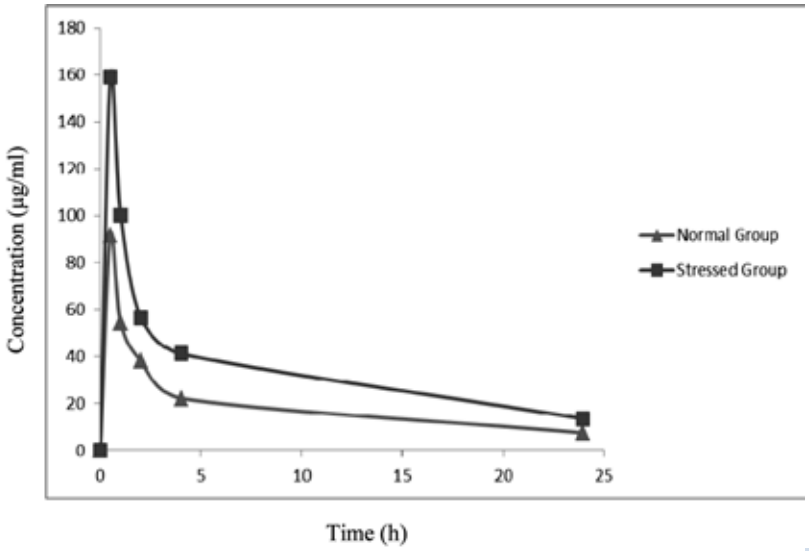

Figure 2. Thiopental's plasma concentration in the normal and stressed chickens at different times

Thiopental pharmacokinetics profiles in the normal and stressed chickens

Thiopental pharmacokinetics profiles in the normal chickens, which include $AUC_{0-\infty}$ (548.93 µg.h/ml), $AUMC_{0-\infty}$ (8046.58 µg.h^2/ml), MRT (14.66 h), $t_{1/2\beta}$ (10.49 h), Cl (0.06 L/h/kg), K_{el} (0.07 h^{-1}), V_{ss} (0.97 L/h/kg), T_{max} (0.5 h) and C_{max} (91.42 µg), while these values changed in the stressed chickens to be (999.55 µg.h/ml), (15573.44 µg.h^2/ml), (15.58 h), (11.36 h), (0.04 L/h/kg), (0.06 h^{-1}), (0.57 L/h/kg), (0.5 h) and (159.01 µg), respectively.

Table 3 shows the pharmacokinetic parameters of thiopental ($AUC_{0-\infty}$, $AUMC_{0-\infty}$, MRT and $t_{1/2\beta}$) were increased in the stressed chickens by 82, 94, 6 and 8%, respectively. On another hand, the Cl, K_{el}, and V_{ss} were decreased in the same group by 33, 14 and 41%, respectively in comparison to the normal group.

Table 3. Pharmacokinetics profiles of thiopental in normal and stressed chickens

Pharmacokinetics parameters	Groups		Effect of OS= H_2O_2-H_2O/ H_2O×100= (%)
	Normal (H_2O) group	Stressed (H_2O_2) group	
$AUC_{0-\infty}$ (µg.h/ml)	548.93	999.55	+82
$AUMC_{0-\infty}$(µg.h^2/ml)	8046.58	15573.44	+94
MRT (h)=AUMC/AUC	14.66	15.58	+6
$t_{1/2\beta}$ (h)	10.49	11.36	+8
Cl (L/h/kg)= dose/AUC	0.06	0.04	-33
K_{el} (h^{-1})= 0.693/ $t_{1/2\beta}$	0.07	0.06	-14
V_{ss} (L/kg)= dose.AUMC/$(AUC)^2$	0.97	0.57	-41
T_{max} (h)	0.50	0.50	0
C_{max} (µg)	91.42	159.01	-74

Tab water was given to the normal chickens while 0.5% H_2O_2 was given to the stress group from 1st to the termination of the experiments at day 14th

Thiopental treatment with dosage of 35 mg/kg, IP for both the normal and stressed chickens

DISCUSSION

The purpose of this study was to use thiopental in chickens for the induction of the general anesthesia and to find out the influence of OS status (induced with H_2O_2) on the thiopental anesthesia, its plasma concentration and pharmacokinetic profile. Thiopental is considered a general anesthetic that stimulates the rapid induction of anesthesia with its increasing the effect of GABA neurotransmitter on the $GABA_A$ receptor which causes depression of the CNS (Clark et al., 2012; Flecknell, 2015; Katzung and Trevor, 2015). Thiopental frequently used as an anesthetic for short surgical operation because it has a good hypnotic effect with occasionally less analgesic and muscle relaxant efficiency (Clark et al., 2012; Katzung and Trevor, 2015) and is considered a safe drug of choice for using in anesthesia because it possesses many benefits including a familiar mechanism of action, less myocardial and cerebral ischemia, decreasing histamine release with a uniquely stable hemodynamic status during anesthesia (Atasoy et al., 1993; Sumitraa et al., 2004; Ninu et al., 2015; Biswas et al., 2017) and was found to have efficient anesthesia than other barbiturates (Ferreira et al., 2013; Shaaban et al., 2018; Brohi et al., 2019). The result of this trial clears up the anesthetic profile of thiopental in the normal and stressed chickens through determining the analgesic and hypnotic ED_{50} values which were decreased in the stressed chickens with H_2O_2 that revealed an increase in thiopental efficacy and possibly increased its toxicity which was in agreement with earlier studies on diazepam sedation (Mousa and Mohammad, 2012a), xylazine analgesia (Mousa and Mohammad, 2012b) and ketamine anesthesia (Mousa, 2014). Thiopental interact and binds to the $GABA_A$/ chloride ionophore receptor complex, thereby enhancing the inhibitory actions of $GABA_A$ in the CNS and this will leads to synaptic inhibition, diminished neuronal excitability, induce anesthesia and lower the nociceptive threshold thus producing the analgesic effect (NCBI, 2020). Thiopental has a mode of action on the CNS (this attributed to reason for choosing it) because of the CNS is more vulnerable to OS status due to its high free radical formation, consuming a lot of oxygen, high amount of unsaturated fatty acids with less antioxidant activity (Pastore et al., 2003). The results show that thiopental plasma concentration was significantly increased with subsequent altering in its pharmacokinetic profile in the stressed chickens compared with the normal chickens. This modification in the thiopental pharmacological response in the stressed chickens attributed to H_2O_2-induced OS and thus causes phar-

macokinetics interaction (Mousa, 2014). H_2O_2-induce OS through its formation of free radicals that break down the vital cell components, especially the protein receptors (Patockova et al., 2003; Sayre et al., 2008), therefore, causes pharmacokinetic interaction by altering the biological constitutes important for absorption, distribution, metabolism and excretion of thiopental that determine the pharmacokinetic profile of thiopental. H_2O_2-induce OS can alter the pharmacokinetic profile of the drugs through its direct and indirect break down of the cell components (especially proteins which included plasma proteins and protein carriers) and thus the organs (liver, kidney, CNS and so on) which have a simultaneous modification at a level of the absorption, distribution, metabolism and excretion of thiopental and so, leading to pharmacokinetics interaction (Chauhan et al., 2020) which is stated here in this study through measuring the pharmacokinetics profile of thiopental indicated by increasing the half-life and decreasing the clearance, elimination rate constant and distribution volume of thiopental of the stress chickens compared to the normal one. The pharmacokinetics interaction has an impact to elevate drug efficacy and subsequent toxicity and this criterion of the drug are an important factor ensuring the drug delivery to the site of action on its target receptor to achieve efficacy and/or improve the preferred therapeutic effect (Wen et al., 2015).

CONCLUSIONS

The outcome of this study reveals the increase of the thiopental pharmacological response affected by H_2O_2-induced OS by increasing its concentration in the plasma and altering the pharmacokinetics profile. We recommended reducing the dose of thiopental to be given to the stressed animals.

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CONFLICT OF INTEREST

None declared by the authors.

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